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Extremely Low-Frequency Magnetic Fields and Childhood Acute Lymphoblastic Leukemia: An Exploratory Analysis of Alternative Exposure Metrics

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Data collected by the National Cancer Institute-Children's Cancer Group were utilized to explore various metrics of magnetic field levels and risk of acute lymphoblastic leukemia (ALL) in children. Cases were aged 0–14 years, were diagnosed with ALL during 1989–1993, were registered with the Children's Cancer Group, and resided in one home for at least 70 percent of the 5 years immediately prior to diagnosis. Controls were identified by using random digit dialing and met the same residential requirements. With 30-second ("spot") measurements and components of the 24-hour measurement obtained in the subject's bedroom, metrics evaluated included measures of central tendency, peak exposures, threshold values, and measures of short-term temporal variability. Measures of central tendency and the threshold measures showed good-to-high correlation, but these metrics correlated less well with the others. Small increases in risk (ranging from 1.02 to 1.69 for subjects in the highest exposure category) were associated with some measures of central tendency, but peak exposures, threshold values, measures of short-term variability, and spot measurements demonstrated little association with risk of childhood ALL. In general, risk estimates were slightly higher for the nighttime (10 p.m.-6 a.m.) interval than for the corresponding 24-hour period. *Am J Epidemiol* 2000;152:20–31.

case-control studies; child; electromagnetic fields; environmental exposure; leukemia, lymphocytic, acute

Several studies have assessed the relation between residential magnetic field exposure and risk of childhood leukemia. Studies with spot or 24-hour measurements of residential magnetic fields have generally provided little evidence of an association with the risk of childhood leukemia. In the absence of a clear carcinogenic mechanism, no single exposure metric can be regarded as a priori most appropriate.

A number of alternative metrics have been proposed (1–3), but few have been tested in epidemiologic studies (4). Data from the largest published study with comprehensive assessment of residential magnetic field levels (5, 6) were used to explore further the relation between different exposure metrics and the risk of childhood acute lymphoblastic leukemia (ALL). More specifically, risk of childhood ALL was evaluated in relation to 1) measures of central tendency, such as mean, 30th, 50th (median), and 70th percentile values for each subject; 2) peak exposures defined as the highest measured values; 3) available measures of short-term temporal variability; 4) threshold values; and 5) spot measurements. The hypothetical nature of the alternative metrics must be recognized due to the lack of any identified biological mechanism of action and the largely negative results of animal studies (3, 7).

MATERIALS AND METHODS

Subjects

The methods used in the National Cancer Institute-Children's Cancer Group (NCI/CCG) investigation of residential 60-Hz magnetic field exposures and risk of ALL in children have been described in detail elsewhere (5, 6). In this exploratory analysis, the subset of subjects evaluated included 515 cases (81 percent of the 638 children aged 0–14 years diagnosed with ALL during 1989–1993, residing in nine midwestern or mid-Atlantic states and participating in the residential magnetic field measurement component of the main NCI/CCG study) and 516 controls (83 percent of the 620 children identified by random digit dialing in the main study (8) and matched individually to cases), who had lived in a single home for at least 70 percent of the reference period. The rationale for this approach was that many of the

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Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; NCI/CCG, National Cancer Institute-Children's Cancer Group; OR, odds ratio.

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exposure metrics described below were originally defined in relation to a subject's residence in a single home; it was unclear how to combine these measures across houses. Thus, the analysis was restricted to the subset of the residentially most stable subjects in the NCI/CCG study.

Subjects with Down's syndrome were excluded from the analyses because prior studies have consistently demonstrated a 10- to 40-fold increased risk of risk of acute leukemia (9) among persons with this congenital disorder. For analyses utilizing a metric derived from the 24-hour residential measurement, the population was further restricted to the 481 cases (75 percent of the 638 cases in the main study) and 431 controls (70 percent of the 620 controls in the main study) with a 24-hour measurement obtained in the child's bedroom.

Magnetic field measurements

A detailed description of the NCI/CCG measurement protocol, based on two studies of personal exposure assessment (10, 11), has been published previously (5). Briefly, for each residence eligible for measurement, a 24-hour measurement was obtained using the Emdex-C meter (Electric Field Measurements, West Stockbridge, Massachusetts) in the child's bedroom. During the 24-hour measurement period, four measurements were made during each minute—at 0, 1, 30, and 31 seconds. The technicians also obtained 30-second "spot" measurements in the center of the subject's bedroom, the room in which the mother slept while pregnant with the subject, the family room, the kitchen, and immediately outside of the front door (within 3 feet (92.1 cm)). The in-home spot measurements were available for 485 cases (94 percent of the 515 cases included in the present investigation) and 437 controls (85 percent of the 516 controls), and the measurements immediately outside the front door were obtained from all participating cases and controls.

Magnetic field measurement metrics

In the primary analysis of the study (6), a time-weighted average of the subject's summary (across all homes) residential magnetic field exposures was calculated from a combination of measurements obtained in the child's bedroom, the family room, and the kitchen and weighted according to the length of residence in each home (and time spent in each room on the basis of data from the first pilot study) (5).

For this report, the arithmetic and geometric means and the 30th, 50th, and 70th percentile values of the 24-hour measurements of the child's bedroom were evaluated. These measures of central tendency reflect more stable levels and are less influenced by transient peak levels. The peak levels assessed included the 90th, 95th, and 99th percentile values and the highest value (designated the 100th percentile) of the 24-hour measurement for each subject. A possible threshold effect was investigated by using the percentage of all measurements during the 24-hour period that exceeded the chosen cutpoints of 0.2, 0.3, and 0.4 µT.

Short-term temporal variability was calculated by using the formula for a rate-of-change metric suggested by Wilson et al. (12). Using the repeated pairs of measurements separated in time by 1 second that were obtained every 30 seconds during the 24-hour bedroom measurement, the first and second of the kth pair of measurements were denoted by $(B_1)_k$ and $(B_2)_k$, respectively. The 1-second, short-term variability, Y_1, was defined by the following equation:

$$Y_1 = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[(B_1)_k - (B_2)_k]^2} \tag{1}$$

where $N = 2{,}880$, the total number of measurement pairs (i.e., a pair of measurements every 30 seconds for a total duration of 24 hours). The 30-second short-term variability, Y_{30}, was defined as:

$$Y_{30} = \sqrt{\frac{1}{N-1}\sum_{k=1}^{N-1}(\bar{B}_{k+1} - \bar{B}_k)^2} \tag{2}$$

$$\bar{B}_k = [(B_1)_k + (B_2)_k]/2.$$

The units for both Y_1 and Y_{30} are magnetic-field level (i.e., µT), which suggests that their values depend not only on the temporal structure of the magnetic field but also on its overall magnitude. Burch et al. (13) have introduced a modified version of Y_{30} that depends only on the temporal structure of this field. This metric is defined by the following equation:

$$Y^*_{30} = \sqrt{\frac{1}{N-1}\sum_{k=1}^{N-1}(\bar{B}_{k+1} - \bar{B}_k)^2} \Bigg/ \sqrt{\frac{1}{N-1}\sum_{k=1}^{N}(\bar{B}_k - \bar{B})^2}, \tag{3}$$

where $\bar{B}_k$ is defined as in equation (2) and $\bar{B}$ is the mean of all 2,880 values of $\bar{B}_k$.

A further measure of short-term variation in magnetic field levels was calculated as the number of consecutive values taken 30 seconds apart that differed by minimum absolute values of 0.03, 0.05, or 0.10 µT (also called the first difference) (14).

Each metric was calculated for the entire 24-hour measurement period as well as for the nighttime period (10 p.m.-6 a.m.), when the subject was most likely to be sleeping in his or her bedroom (15).

The coherence hypothesis was also evaluated. Coherence refers to the requirement that magnetic fields must be relatively constant over time periods of 1–10 seconds to affect biologic systems (16, 17). The hypothesis suggests that coherence should be a modifying variable for the relation between magnetic field magnitude and occurrence of disease. Support for the hypothesis derives from a study of electric utility workers in which effects on melatonin levels were associated with the interaction between short-term variability and the geometric mean magnetic field measurements (13).

Some investigators have suggested the possibility of windows in the dose-response relation, e.g., intervals of field strength that exclusively increase risk (18).

Other risk factors

Information about demographic and socioeconomic factors was ascertained in the telephone interview conducted by the Children's Cancer Group (5). Lifetime residential history and residential characteristics were obtained in a second telephone interview of mothers of the subset of cases and controls included in the NCI/CCG residential magnetic field exposure assessment component (5, 19).

Statistical methods

For evaluation of relations among the various metrics and types of metrics defined, Pearson correlation coefficients were calculated (20). Magnetic field exposures based on percentile values across subjects were categorized similarly to earlier epidemiologic studies of residential magnetic field exposures, in which subjects with measurements below the median (0–49th percentile) served as the referent and subjects with higher exposures were classified into three smaller groups (50th–74th, 75th–89th, and 90–100th percentiles) (21, 22). Quartiles were also used, as is commonly done for analyses of other types of exposure.

Interaction terms between short-term variability and the geometric mean and other measures of the central tendency (including the 30th–70th percentiles for the 24-hour measurements and the 10 p.m.-6 a.m. component of the 24-hour period) (15–17) were included in models in order to evaluate the coherence hypothesis. The possibility of windows in the dose-response relation (18) was examined by statistical tests for linearity between the various magnetic field metrics.

Data analyses utilized unconditional and conditional logistic regression methods (23). Age, sex, mother's education, and family income were used as covariates. The basic logistic model with the covariates provided an adequate fit, with some tendency toward overdispersion (deviance = 1,390 and Pearson chi-square = 1,023, with 1,014 df). Tests for heterogeneity and linear trend were performed by using the likelihood ratio test for continuous and categorical explanatory variables (23). Departure from linearity was tested by adding a categorical variable to a model that already included the continuous version of the factor. All significance levels reported are two sided, and no adjustments were used for multiple comparisons. Confidence intervals were calculated by using the profile likelihood method (24).

Because of improved precision (there were only 330 matched pairs among the 515 cases and 516 controls residing in one home for at least 70 percent of the reference period and only 262 matched pairs among the 481 cases and 431 controls residing in a single residence with a 24-hour measurement in the child's bedroom), the results are presented using unconditional logistic regression. Results were largely similar when the same metrics were evaluated using conditional logistic regression for matched pairs (data not shown). The odds ratios in the conditional logistic regression analyses tended to be slightly higher, although confidence intervals were considerably wider.

RESULTS

Cases were similar to controls for most potential confounders except for family income and, to a lesser extent, mother's education (table 1). No clear case-control differences were observed for birth order, number of siblings, mother's age at birth of the subject, or residential characteristics.

Correlation of magnetic field exposure metrics

Pearson correlation coefficients ranged from poor to extremely high (from R = 0.22–0.99). Good-to-extremely high correlation was observed among the measures of central tendency (R = 0.85–0.99) and the threshold measures (R = 0.73–0.87), but lower correlations were seen between these two types of measures and the peak values, the rate-of-change metrics, the measures of short-term variability, and the front-door spot measurements (table 2). Because concerns have been raised about the risk of childhood leukemia in relation to metrics other than those of central tendency, risk estimates are shown for each of the various metrics in tables 3–7.

Measures of central tendency

Measures of central tendency (all derived from components of the 24-hour magnetic field measurement of the child's bedroom, although the time-weighted average metrics also included the spot measurement data from the family room and the kitchen) were generally slightly higher for cases than for controls; this case-control difference was somewhat more pronounced for the nighttime period (10 p.m.-6 a.m.) (table 3). When evaluated using categorical approaches, odds ratios for ALL were generally below 1.4 for the entire 24-hour period and slightly higher for the nighttime interval among children whose summary home magnetic field levels were in the highest exposure group (90th-100th percentiles) (table 3). For children in the highest exposure category, the greatest risks for childhood ALL were associated with the 30th percentile measurements (odds ratio (OR) = 1.39 for the 24-hour period; OR = 1.69 for 10 p.m.-6 a.m.). Lower risks were seen for measurements in higher percentile categories. The risk estimates of 1.30 or greater characterizing subjects in the highest exposure category generally had similar confidence intervals (table 3). When the measures of central tendency were evaluated as continuous variables, weak, significantly increasing trends were observed. No statistically significant interactions with age or sex were found, and the risk estimates for subjects aged 0–3 years were similar to or lower than those for older children (data not shown).

TABLE 1. Distribution of selected characteristics for 478 childhood acute lymphoblastic leukemia cases and 426 controls*, nine-state US study, 1989–1993

Factor	Cases		Controls	
	No.	%	No.	%
Sex				
Male	244	51	228	54
Female	234	49	198	46
Age (years)				
0–1	49	10	59	14
2–4	222	46	180	42
5–9	130	27	130	31
10–15	77	16	57	13
Mother's age at subject's birth (years)				
15–20	23	5	23	5
21–25	121	25	92	22
26–30	194	41	175	41
31–45	140	29	136	32
No. of siblings				
0	61	13	42	10
1	216	45	162	38
2	114	24	154	36
≥3	87	18	68	16
Birth order				
First	161	34	163	38
Second	194	41	135	32
Third or higher	123	26	128	30
Mother's education				
12 years or less, high school graduate	174	36	175	41
Post-high school and some college	170	36	115	27
College graduate or more	134	28	136	32
Family income in reference year (dollars)				
<$20,000	65	14	37	9
$20,000–$29,999	78	16	52	12
$30,000–$39,999	107	22	69	16
$40,000–$49,999	81	17	86	20
≥$50,000	147	31	182	43
Type of residence				
Single-family home	404	85	369	87
Apartment	24	5	18	4
Other	50	10	39	9
Home ownership status				
Owned home	402	84	382	90
Rented home	65	14	37	9
Other	8	2	4	1
Unknown	3	<1	3	<1
Degree of urbanization				
Urban	114	24	85	20
Suburban	211	44	202	47
Rural/farm	153	32	139	33

* Excludes three cases and five controls missing information on family income among 481 cases and 431 controls with a 24-hour bedroom measurement.

TABLE 2. Pearson correlation coefficients of selected exposure metrics of residential magnetic field exposure for the combined group of 478 cases and 426 controls, nine-state US study, 1989–1993

Selected exposure metrics	Selected exposure metrics																	
	TWA 24 hrs*	TWA 10–6*	Mean 24 hrs*	Geo-metric mean 24 hrs*	Median 24 hrs*	Median 10–6*	30th per-centile 24 hrs*	30th per-centile 10–6*	90th per-centile 24 hrs*	95th per-centile 24 hrs*	100th per-centile 24 hrs*	>0.2 µT 24 hrs*	>0.3 µT 24 hrs*	>0.4 µT 24 hrs*	RCM, 30 seconds 24 hrs*	Modified RCM 30 sec-onds*	No. of peaks >0.3 µT 24 hrs*	Front door spot*
TWA 24 hrs	1.00	0.97	0.97	0.96	0.94	0.89	0.93	0.86	0.85	0.84	0.57	0.83	0.83	0.81	0.54	–0.41	0.56	0.62
TWA 10–6	0.97	1.00	0.95	0.94	0.90	0.94	0.90	0.93	0.83	0.81	0.54	0.80	0.81	0.79	0.51	–0.38	0.51	0.60
Mean 24 hrs	0.97	0.95	1.00	0.97	0.94	0.91	0.94	0.88	0.90	0.89	0.60	0.83	0.85	0.84	0.60	–0.40	0.56	0.53
Geometric mean 24 hrs	0.96	0.94	0.97	1.00	0.98	0.92	0.98	0.90	0.78	0.77	0.53	0.85	0.86	0.84	0.38	–0.39	0.55	0.56
Median 24 hrs	0.94	0.90	0.94	0.98	1.00	0.89	0.98	0.85	0.74	0.73	0.51	0.86	0.87	0.83	0.43	–0.38	0.56	0.55
Median 10–6	0.89	0.94	0.91	0.92	0.89	1.00	0.88	0.98	0.73	0.71	0.48	0.77	0.80	0.80	0.38	–0.33	0.47	0.50
30th percentile 24 hrs	0.93	0.90	0.94	0.98	0.98	0.88	1.00	0.86	0.72	0.71	0.49	0.84	0.85	0.83	0.39	–0.37	0.56	0.56
30th percentile 10–6	0.86	0.93	0.88	0.90	0.85	0.98	0.88	1.00	0.70	0.68	0.44	0.73	0.76	0.77	0.32	–0.32	0.40	0.50
90th percentile 24 hrs	0.85	0.83	0.90	0.78	0.74	0.73	0.72	0.70	1.00	0.96	0.63	0.67	0.69	0.69	0.80	–0.35	0.52	0.41
95th percentile 24 hrs	0.84	0.81	0.89	0.77	0.73	0.71	0.71	0.68	0.96	1.00	0.65	0.66	0.68	0.68	0.80	–0.37	0.54	0.39
100th percentile 24 hrs	0.57	0.54	0.60	0.53	0.51	0.48	0.49	0.44	0.63	0.65	1.00	0.46	0.46	0.45	0.76	–0.13	0.48	0.28
>0.2 µT 24 hrs	0.83	0.80	0.83	0.85	0.86	0.77	0.84	0.73	0.67	0.66	0.46	1.00	0.87	0.73	0.41	–0.34	0.60	0.52
>0.3 µT 24 hrs	0.83	0.81	0.85	0.86	0.87	0.80	0.85	0.76	0.69	0.68	0.46	0.87	1.00	0.92	0.41	–0.27	0.54	0.47
>0.4 µT 24 hrs	0.81	0.79	0.84	0.84	0.83	0.80	0.83	0.77	0.69	0.68	0.45	0.73	0.92	1.00	0.40	–0.22	0.46	0.41
RCM 30 seconds 24 hrs	0.54	0.51	0.60	0.45	0.43	0.38	0.39	0.32	0.80	0.80	0.76	0.41	0.41	0.40	1.00	–0.11	0.58	0.22
Modified RCM 30 seconds	–0.41	–0.38	–0.40	–0.39	–0.38	–0.73	–0.37	–0.32	–0.35	–0.37	–0.13	–0.34	–0.27	–0.22	–0.11	1.00	–0.13	–0.28
No. of peaks >0.03 µT 24 hrs	0.56	0.51	0.56	0.55	0.56	0.47	0.50	0.40	0.52	0.54	0.48	0.60	0.54	0.46	0.58	–0.13	1.00	0.31
Front door spot	0.62	0.60	0.53	0.56	0.55	0.50	0.56	0.50	0.41	0.39	0.28	0.52	0.47	0.41	0.22	–0.28	0.31	1.00

* TWA, weighted average of the magnetic field levels during the 24-hour period in the child's bedroom, the kitchen, and the family room (6); TWA 10–6, weighted average from 10 p.m. to 6 a.m. in the child's bedroom, the kitchen, and the family room; mean 24 hrs, mean 24-hour measurement in the child's bedroom; geometric mean 24 hrs, geometric mean 24-hour measurement in the child's bedroom; median 24 hours, 24-hour measurement in the child's bedroom; median 10–6, mediian of the measurement from 10 p.m. to 6 a.m. in the child's bedroom; geometric mean 30th 24 hrs, 30th percentile of the 24-hour measurement in the child's bedroom; 30th percentile 10–6, 30th percentile of the measurement from 10 p.m. to 6 a.m. in the child's bedroom; 90th, 95th, and 100th percentiles 24 hrs, 90th, 95th, and 100th percentiles, respectively, of the 24-hour measurement in the child's bedroom; >0.2 µT, >0.3 µT, and >0.4 µT 24 hrs, percentage of all measurements in the child's bedroom during the 24-hour period that exceeded thresholds of >0.2 µT, >0.3 µT, and >0.4 µT, respectively; RCM (rate of change metric) 30 seconds 24 hrs, 30-second, short-term variability metric Y_{30} during the 24-hour measurement in the child's bedroom, as defined by equation 2 in the text; modified RCM 30 seconds, 30-second, short-term variability metric Y^{*}_{30} during the 24-hour measurement in the child's bedroom that depends only on the temporal structure of the magnetic field and is defined by equation 3 in the text; no. of peaks >0.03 µT 24 hrs, the number of consecutive measurements, taken 30 seconds apart during the 24-hour measurement of the child's bedroom that differed by a minimum absolute value of 0.03 µT; front door spot (normal power), a consecutive series of 30 measurements taken at 1-second intervals during a 30-second period of time immediately outside the front door of the residence (within 3 feet (92.1 cm)) when home appliances were in the typical usage mode.

TABLE 3. Risk of childhood acute lymphoblastic leukemia associated with central tendency of residential magnetic field exposures, adjusted for age, sex, mother's education, and family income*, nine-state US study, 1989–1993

Metric	Percentiles						Continuous†		
	0–49‡ (OR§)	50–74 (OR)	75–89 (OR)	90–100		*p* for trend	OR	95% CI	*p*
				OR	95% CI§				
Time-weighted average¶									
24 hrs	1	1.09	1.13	1.02	0.66, 1.57	0.66	1.07	0.95, 1.20	0.27
10–6	1	1.10	1.09	1.15	0.75, 1.77	0.45	1.07	0.96, 1.21	0.24
Mean§									
24 hrs	1	1.03	1.40	1.35	0.85, 2.16	0.09	1.11	0.99. 1.26	0.09
10–6	1	1.26	1.24	1.44	0.90, 2.31	0.08	1.13	1.00, 1.29	0.06
Geometric mean§									
24 hrs	1	1.28	1.36	1.39	0.82, 2.08	0.08	1.12	1.02, 1.35	0.03
10–6	1	1.36	1.21	1.56	0.98, 2.51	0.04	1.17	1.02, 1.36	0.02
30th percentile§									
24 hrs	1	1.10	1.22	1.39	0.87, 2.23	0.12	1.23	1.04, 1.47	0.01
10–6	1	1.04	1.16	1.69	1.05, 2.74	0.05	1.20	1.03, 1.43	0.02
50th percentile (median)§									
24 hrs	1	1.14	1.42	1.28	0.81, 2.05	0.09	1.14	1.00, 1.31	0.05
10–6	1	1.17	1.21	1.50	0.94, 2.46	0.07	1.14	1.00, 1.32	0.04
70th percentile§									
24 hrs	1	1.03	1.18	1.44	0.90, 2.33	0.12	1.11	1.00, 1.24	0.04
10–6	1	1.12	1.34	1.47	0.92, 2.36	0.05	1.14	1.02, 1.29	0.02

* For 478 cases and 426 controls unless otherwise indicated.
† Per μT.
‡ Reference category.
§ OR, odds ratio; CI, confidence interval; mean 24 hrs, mean 24-hour measurement in the child's bedroom; mean 10–6, mean of the measurement from 10 p.m. to 6 a.m. in the child's bedroom; geometric mean 24 hrs, geometric mean 24-hour measurement in the child's bedroom; geometric mean 10–6, geometric mean of the measurement from 10 p.m. to 6 a.m. in the child's bedroom; 30th percentile 24 hrs, 30th percentile of the 24-hour measurement in the child's bedroom; 30th percentile 10–6, 30th percentile of the measurement from 10 p.m. to 6 a.m. in the child's bedroom; 50th percentile (median) 24 hrs, median 24-hour measurement in the child's bedroom; 50th percentile (median) 10–6, median of the measurement from 10 p.m. to 6 a.m in the child's bedroom; 70th percentile 24 hrs, 70th percentile of the 24-hour measurement in the child's bedroom; 70th percentile 10–6, 70th percentile of the measurement from 10 p.m. to 6 a.m. in the child's bedroom.
¶ The time-weighted average for 512 cases and 511 controls (excludes three cases and five controls missing family income among 515 cases and 516 controls residing in one home for 70% or more of the reference period) was a weighted average of the magnetic field levels in the child's bedroom, the family room, and the kitchen (6). Time-weighted average 24 hrs, time-weighted average of the 24-hour measurement in the child's bedroom; time-weighted average 10-6, time-weighted average of the measurement from 10 p.m. to 6 a.m. in the child's bedroom.

Peak exposures

In categorical analyses of ALL risks in relation to peak magnetic flux density, an increased trend was found for two of eight peak value metrics (the 90th and 95th percentiles during the 10 p.m.-6 a.m. nighttime period), although none of the odds ratios were greater than 1.5 (table 4). No significant trends in risk were observed when exposures were assessed in quartiles (data not shown). The odds ratios were close to unity when peak values were evaluated as continuous variables.

Threshold exposures

Using threshold values of more than 0.2, more than 0.3, and more than 0.4 μT, no clear trend was observed across categories (table 5). The number of zero values in the highest categories was such that some categories had to be collapsed to calculate the risks. While there was a slight tendency toward higher risks with increasing threshold values, the odds ratios were below 1.5 for the subjects with the highest measured values. The odds ratios were nonsignificantly elevated (range, 1.15–1.24) when magnetic field levels were assessed for the entire 24-hour period, and ALL risks were similar for the nighttime interval. Risks of childhood ALL were significantly elevated, however, when field levels were evaluated as continuous variables for threshold values exceeding 0.3 μT.

Rate-of-change metrics

A weak inverse correlation was found between the rate-of-change indices used to reflect short-term temporal variability, which attained statistical significance for the modified rate-of-change metric for the nighttime (table 6). No clear trends emerged across categories for other rate-of-change indices. Risk estimates were close to unity in the analyses examining the number of peaks above specified thresholds using continuous variables.

For the metrics demonstrating the strongest association with risk of childhood ALL (such as the 30th percentile nighttime measurement), there was no significant interaction with the inverse modified rate-of-change metric. The relative risks (relative to the lowest quartile of the 30th percentile nighttime measurement and the lowest quartile of the inverse modified

TABLE 4. Risk of childhood acute lymphoblastic leukemia associated with peak values, adjusted for age, sex, mother's education, and family income for 478 cases and 426 controls*, nine-state US study, 1989–1993

Metric	Percentiles						Continuous†		
	0–49‡ (OR§)	50–74 (OR)	75–89 (OR)	90–100		*p* for trend	OR	95% CI	*p*
				OR	95% CI§				
90th percentile§									
24 hrs	1	0.90	1.33	1.27	0.80, 2.04	0.17	1.02	0.96, 1.09	0.53
10–6	1	1.20	1.45	1.40	0.88, 2.25	0.04	1.02	0.96, 1.10	0.53
95th percentile§									
24 hrs	1	1.04	1.24	1.17	0.73, 1.86	0.30	1.01	0.96, 1.07	0.77
10–6	1	1.15	1.42	1.44	0.90, 2.31	0.04	1.03	0.97, 1.10	0.40
99th percentile§									
24 hrs	1	1.04	1.45	1.03	0.65, 1.63	0.31	1.01	0.97, 1.06	0.63
10–6	1	1.14	1.20	1.33	0.84, 2.13	0.16	1.02	0.96, 1.08	0.52
Peak (100th percentile)§									
24 hrs	1	1.04	1.31	1.11	0.70, 1.76	0.32	0.99	0.97, 1.02	0.66
10–6	1	1.08	1.17	1.15	0.73, 1.84	0.39	1.00	0.96, 1.04	0.91

* Excludes three cases and five controls missing information on family income among 481 cases and 431 controls with a 24-hour measurement.

† Per μT.

‡ Reference category.

§ OR, odds ratio; CI, confidence interval; 90th percentile 24 hrs, 90th percentile of the 24-hour measurement in the child's bedroom; 90th percentile 10–6, 90th percentile of the measurement from 10 p.m. to 6 a.m in the child's bedroom; 95th percentile 24 hrs, 95th percentile of the 24-hour measurement in the child's bedroom; 95th percentile 10–6, 95th percentile of the measurement from 10 p.m. to 6 a.m in the child's bedroom; 99th percentile 24 hrs, 99th percentile of the 24-hour measurement in the child's bedroom; 99th percentile 10–6, 99th percentile of the measurement from 10 p.m. to 6 a.m in the child's bedroom; peak (100th percentile) 24 hrs, the highest value of the 24-hour measurement in the child's bedroom; peak (100th percentile) 10–6, the highest value of the measurement from 10 p.m. to 6 a.m. in the child's bedroom.

TABLE 5. Risk of childhood acute lymphoblastic leukemia with threshold values of residential magnetic field exposure, adjusted for age, sex, mother's education, and family income for 478 cases and 426 controls*, nine-state US study, 1989–1993

Metric	Percentiles						Continuous†		
	OR‡	OR	OR	OR	95% CI‡	*p* for trend	OR	95% CI	*p*
Threshold levels	0–57th percentiles§	58th–74th percentiles	75th–89th percentiles	90th–100th percentiles					
>0.2 μT, 24 hrs‡	1	0.90	1.15	1.23	0.78, 1.97	0.34	1.004	0.999, 1.009	0.13
	0–68th percentiles§	69th–74th percentiles	75th–89th percentiles						
>0.2 μT, 10–6‡	1	0.97	1.09	1.42	0.90, 2.26	0.18	1.005	0.999, 1.010	0.08
	0–74th percentiles§		75th–89th percentiles						
>0.3 μT, 24 hrs‡	1		1.06	1.26	0.80, 2.00	0.33	1.007	0.999, 1.014	0.08
	0–79th percentiles§		80th–89th percentiles						
>0.3 μT, 10–6‡	1		1.05	1.25	0.79, 1.97	0.36	1.088	1.000, 1.016	0.04
>0.4 μT, 24 hrs‡	1		1.15	1.14	0.73, 1.80	0.46	1.009	0.999, 1.020	0.07
	0–86th percentiles§			87th–100th percentiles					
>0.4 μT, 10–6‡	1			1.20	0.81, 1.78	0.36	1.010	0.999, 1.021	0.07

* Excludes three cases and five controls missing information on family income among 481 cases and 431 controls with a 24-hour bedroom measurement.

† Per percent measured values exceeding the threshold level.

‡ OR, odds ratio; CI, confidence interval; threshold levels >0.2 μT, >0.3 μT, >0.4 μT, 24 hrs, percentage of all measurements in the child's bedroom during the 24-hour period that exceeded thresholds of >0.2 μT, >0.3 μT, or >0.4 μT, respectively; threshold levels >0.2 μT, >0.3 μT, >0.4 μT, 10–6, percentage of all measurements in the child's bedroom during 10 p.m. to 6 a.m that exceeded thresholds of >0.2 μT, >0.3 μT, or >0.4 μT, respectively.

§ Reference category.

TABLE 6. Risk of childhood acute lymphoblastic leukemia associated with short-term, temporal variability, adjusted for age, sex, mother's education, and family income for 478 cases and 426 controls unless otherwise indicated*, nine-state US study, 1989–1993

Metric	Percentiles						Continuous†		
	0–49‡ (OR§)	50–74 (OR)	75–89 (OR)	90–100		*p* for trend	OR	95% CI	*p*
				OR	95% CI§				
Rate of change§									
1 second, 24 hrs	1	1.14	1.23	0.93	0.58, 1.48	0.72	0.46	0.10, 1.76	0.26
1 second, 10–6	1	0.93	0.98	0.99	0.62, 1.58	0.89	0.37	0.06, 1.99	0.25
30 seconds, 24 hrs	1	1.17	1.44	0.86	0.54, 1.37	0.61	0.80	0.46, 1.29	0.36
30 seconds, 10–6	1	1.03	1.34	0.95	0.60, 1.52	0.57	0.81	0.42, 1.40	0.47
Modified rate of change§									
30 seconds, 24 hrs	1	0.93	0.95	0.83	0.52, 1.32	0.47	0.82	0.50, 1.34	0.43
30 seconds, 10–6	1	1.05	0.81	0.68	0.42, 1.07	0.08	0.66	0.43, 1.00	0.05
No. of peaks§									
≥0.03 μT, 24 hrs	1	0.87	1.42	0.98	0.62, 1.58	0.48	0.998	0.983, 1.014	0.83
≥0.03 μT,10–6	1	1.09	1.18	0.96	0.60, 1.54	0.74	0.996	0.978, 1.015	0.70
≥0.05 μT, 24 hrs	1	0.98	1.30	0.97	0.61, 1.56	0.60	0.997	0.973, 1.023	0.83
≥0.05 μT, 10–6	1	1.01	1.12	0.98	0.62, 1.56	0.81	0.993	0.963, 1.024	0.65
≥0.1 μT, 24 hrs	1	1.11	1.07	0.91	0.57, 1.44	0.95	0.997	0.947, 1.052	0.92
	0–74‡ (OR)		75–89 (OR)						
≥0.1 μT, 10–6	1		1.11	0.77	0.49, 1.22	0.48	0.997	0.933, 1.067	0.93

* Excludes three cases and five controls missing information on family income among 481 cases and 431 controls with a 24-hour measurement.

† With 476 cases and 426 controls (excludes two cases who had no variability in measurement during 10 p.m. to 6 a.m.).

‡ Reference category.

§ OR, odds ratio; CI, confidence interval; >0.3 μT, >0.5 μT, >0.1 μT, 24 hrs, percentage of all measurements in the child's bedroom during the 24-hour period that exceeded thresholds of >0.3 μT, >0.5 μT, and >0.1 μT, respectively; >0.3 μT, >0.5 μT, 10–6, percentage of all measurements in the child's bedroom from 10 p.m. to 6 a.m.; rate of change, 1 second, 24 hours, 1-second, short-term variability metric Y_1 during the 24-hour measurement in the child's bedroom, as defined by equation 1 in the text; rate of change, 1 second, 10–6, 1-second, short-term variability metric Y_1 during 10 p.m.–6 a.m. in the child's bedroom, as defined by equation 1 in the text; rate of change, 30 seconds, 24 hours, 30-second, short-term variability metric Y_{30} during the 24-hour measurement in the child's bedroom, as defined by equation 2 in the text; rate of change, 30 seconds, 10–6, 30-second, short-term variability metric Y_{30} during 10 p.m.–6 a.m. in the child's bedroom, as defined by equation 2 in the text; modified rate of change, 30 seconds, 24 hrs, 30-second, short-term variability metric Y^*_{30} during the 24-hour measurement in the child's bedroom that depends only on the temporal structure of the magnetic field and is defined by equation 3 in the text; modified rate of change, 30 seconds, 10–6, 30-second, short-term variability metric Y^*_{30} during 10 p.m.–6 a.m. in the child's bedroom that depends only on the temporal structure of the magnetic field and is defined by equation 3 in the text; no. of peaks ≥0.03, ≥0.05, and ≥0.1 μT, 24 hrs, number of consecutive measurements taken 30 seconds apart during the 24-hour measurement in the child's bedroom that differed by a minimum absolute value of ≥0.03, ≥0.05, or ≥0.1 μT; no. of peaks ≥0.03, ≥0.05, and ≥0.1 μT, 10–6, number of consecutive measurements taken 30 seconds apart during 10 p.m.–6 a.m in the child's bedroom that differed by a minimum absolute value of ≥0.03, ≥0.05, or ≥0.1 μT.

rate-of-change metric) for the highest quartile of nighttime 30th percentile by increasing quartiles of the nighttime modified rate-of-change metric were as follows: OR = 1.2 (95 percent confidence interval (CI): 0.2, 5.6), OR = 1.6 (95 percent CI: 0.7, 3.5), OR = 1.3 (95 percent CI: 0.7, 2.3), and OR = 1.5 (95 percent CI: 0.9, 2.5). The estimated risk for the continuous interaction term for these two variables was OR = 1.07 (95 percent CI: 0.96, 1.26) (data not shown). There was little evidence of interactions when the same analyses were carried out to evaluate possible interactions of the inverse modified rate-of-change metric with other measures of central tendency.

Spot measurements

No apparent associations were observed for any of the high- or low-power spot measurements and the risk of childhood ALL (table 7).

Magnetic field exposure windows

Evaluation of the possibility of nonmonotonic dose-response relations for magnetic field intensity and risk of childhood ALL revealed no evidence for departure from linearity for any of the magnetic field strength indices (data not shown).

DISCUSSION

This paper presents the results of an exploratory analysis of a large case-control study of childhood ALL and magnetic field exposure. The results should be interpreted with caution because of the hypothesis-generating nature of the analysis and because of the large number of analyses and statistical tests performed. It should be possible to evaluate the metrics we have examined within other populations in

TABLE 7. Risk of childhood acute lymphoblastic leukemia associated with spot measurements of residential magnetic field exposure, adjusted for age, sex, mother's education, and family income, nine-state US study, 1989–1993

Spot measurements (room)*	No. of subjects (cases + controls)†	Percentiles						Continuous‡		
		0–49§ (OR¶)	50–74 (OR)	75–89 (OR)	90–100		p for trend	OR	95% CI	p
					OR	95% CI¶				
Child's bedroom (normal power)	478 + 425	1	1.04	1.45	1.32	0.84, 2.11	0.07	1.10	0.98, 1.26	0.11
Child's bedroom (low power)	478 + 423	1	1.03	1.39	1.11	0.70, 1.77	0.26	1.08	0.95, 1.24	0.25
Pregnancy bedroom (normal power)	350 + 319	1	0.73	1.40	1.22	0.71, 2.11	0.35	1.11	0.96, 1.30	0.16
Pregnancy bedroom (low power)	350 + 318	1	0.91	1.03	1.15	0.67, 2.00	0.71	1.03	0.89, 1.19	0.74
Family room (normal power)	478 + 425	1	1.13	1.24	0.99	0.63, 1.57	0.56	1.04	0.93, 1.17	0.46
Family room (low power)	478 + 424	1	1.18	1.22	0.91	0.58, 1.45	0.76	1.01	0.90, 1.14	0.84
Kitchen (normal power)	478 + 425	1	0.97	1.19	1.43	0.90, 2.29	0.13	1.05	0.95, 1.15	0.34
Kitchen (low power)	478 + 423	1	1.00	1.39	1.13	0.71, 1.80	0.23	1.05	0.93, 1.18	0.44
Front door	478 + 426	1	1.22	1.14	1.28	0.83, 1.97	0.21	1.07	0.98, 1.17	0.13

* Spot measurements child's bedroom, pregnancy bedroom (the bedroom where the mother slept at least half of her pregnancy with the index child), family room (defined as the room in the home where the index child typically spent the largest period of time each day except for his or her bedroom), kitchen, and front door (normal power), a consecutive series of 30 measurements taken at 1-second intervals during a 30-second period of time in the child's bedroom, pregnancy bedroom, family room, kitchen, or immediately outside the front door of the residence (within 3 feet (92.1 cm)) when home appliances were in typical usage mode; spot measurements child's bedroom, pregnancy bedroom, family room, and kitchen (low power), a consecutive series of 30 measurements taken at 1-second intervals during a 30-second period in the same rooms as described above when all home appliances except for three lights were turned off.

† The numbers of cases and controls listed for each room and type of measurement exclude those missing spot measurements for that room or type of measurement among a maximum of 478 cases and 426 controls with a 24-hour bedroom measurement and family income information.

‡ Per μT.

§ Reference category.

¶ OR, odds ratio; CI, confidence interval.

current or previously completed epidemiologic studies of residential magnetic field exposure and childhood leukemia.

Despite the wide range in the correlation coefficients among the various exposure metrics, good-to-extremely high correlation was seen among the measures of central tendency and the threshold measures. The great range in correlation coefficients was *not* paralleled by a corresponding wide range in the risk estimates. Overall, the risk of childhood ALL associated with the various exposure metrics ranged from OR = 0.68 (95 percent CI: 0.42, 1.07) to 1.69 (95 percent CI: 1.05, 2.74) for children in the highest exposure category using categorical measures and from OR = 0.37 (95 percent CI: 0.06, 1.99) to 1.23 (95 percent CI: 1.04, 1.47) using continuous measures. In general, childhood ALL risks for subjects in the highest exposure category were slightly higher for the nighttime interval than for the corresponding 24-hour period for measures of central tendency. The risks associated with the measures of central tendency were very highly correlated with each other. Thus, many of the same homes are included in the highest exposure category for all measures of central tendency, and the results of the case-control analyses presented in table 3 are generally very similar. There was little evidence of significant associations for peak exposures, thresholds, measures of short-term variability, or spot measurements. Only one measure of short-term variability (modified rate of change at nighttime) showed a borderline significant inverse relation with leukemia risk. The absence of any other associations with measures of temporal variability suggests that this single finding is probably due to chance.

Results of correlation between two metrics do not always predict the corresponding risks. For example, a very high correlation ($R = 0.97$) was seen between the 24-hour, time-weighted average and the 24-hour mean. However, the risks for childhood ALL differed somewhat for these two measures of central tendency in the categorical analyses. The odds ratio was estimated as 1.02 (95 percent CI: 0.66, 1.57) (p for trend = 0.66) for children in the highest exposure category using the 24-hour, time-weighted average, whereas the odds ratio estimate was 1.35 (95 percent CI: 0.85, 2.16, p for trend = 0.09) for children in the highest exposure category using the 24-hour mean.

The results of the multivariate analyses to assess potential interaction of the modified rate of change and the 30th–70th percentiles for the 24-hour and the nighttime periods revealed little evidence of interaction. Thus, the data from the NCI/CCG study do not provide epidemiologic support for either the laboratory experimental results of Litovitz et al. (16) and Farrell et al. (17) or the worker data on melatonin excretion reported by Burch et al. (13).

In the NCI/CCG study, residential magnetic field measurements were obtained from larger numbers of subjects and represented more complete coverage of subjects' residential history than for populations evaluated in all previously published reports. Residential magnetic field levels have been measured in only seven other studies of childhood leukemia (21, 25–30), and 24-hour or longer measurements were obtained in children's bedrooms in only three of these investigations (21, 28, 29). Long-term measurements provide obvious advantages over spot measurements, including increased accuracy and the possibility for assessing temporal variability. Unlike proxy measures, direct residential measurements provide information on all sources of magnetic fields, including electrical appliances, grounding systems, and in-house wiring as well as exposures from nearby power lines. Although a 24-hour measurement reflects concurrent exposure more precisely than do spot measurements or wire coding, it is not known how each of these approaches correlates with or represents historical or long-term exposures.

Retrospective magnetic field exposure assessment is exceedingly difficult. As stated in a recent review, "exposure assessment is the most critical and least understood element of these studies of electric and magnetic fields" (31, p. 273). The measurement protocol for the NCI/CCG study was derived from two pilot studies, in which personal monitoring data were obtained from young children and compared with extensive residential, school, and day care area measurements to identify the subset of residential area magnetic field measurements that correlated well with personal exposures of young children (5, 6, 10, 11). In addition, wire code designations were found to be as good a proxy for magnetic field levels in the NCI/CCG study as in previous studies utilizing wire codes (32).

The time lag between diagnosis and measurements in the NCI/CCG study (with most measurements taken within 24 months of diagnosis) was shorter than in all but one (29) case-control study. Measurements obtained as soon as possible after diagnosis are likely to represent a better estimate of past exposures than are measurements taken several years to decades after diagnosis. Nonetheless, retrospective estimates of past exposures are always problematic. There are few studies that provide information about temporal aspects of residential magnetic field levels or other characteristics over periods of several years. In addition, weaknesses of the NCI/CCG residential magnetic field measurement study included lack of participation by 22 percent of the eligible cases and 37 percent of the eligible controls and differences between cases and controls in family income (and, to a lesser extent, mother's education) due to use of random digit dialing. In our investigation as well as in all other case-control studies that have included in-home residential magnetic field measurements (21, 26, 28–30), refusal rates have been higher for eligible controls than for cases; thus, the results of all of the studies may be affected by potential selection bias. The population included in this evaluation represented a large subset of that described in the main NCI/CCG study (6) and was very similar in most respects, although the subset was more residentially stable and slightly more likely to live in single-family homes, and a higher proportion of families of the subjects owned their own home. It can be argued, however, that there is less measurement error (more reliability) for subjects living in only one home during the reference period

In this investigation, a number of exposure metrics were evaluated using several cutoff levels. Our findings were consistent with studies in Los Angeles, California (21), Canada (29), and Germany (15, 28) reporting nonsignificantly elevated odds ratios between arithmetic mean (21, 29) or median summary values (15, 28) of the 24-hour measurement (or 48-hour measurement in Canada) in the child's bedroom and risk of childhood leukemia. Similar to the findings from two case-control studies in North America, the risk of childhood leukemia in the NCI/CCG study did not vary substantially in relation to other metrics, although detailed comparisons were somewhat limited to the data reported for the other specific metrics evaluated.

In contrast to the findings from the German study, we could not confirm a closer association between the median of the 24-hour child's bedroom measurement and risk of childhood leukemia among cases less than age 4 years at diagnosis, even though the number of exposed subjects in our study was much larger than that in the German study. In fact, there were 100 subjects with a median magnetic flux density above 0.2 μT in the NCI/CCG study, more than five times the number in the German study. The main justification for using medians instead of means has been lower sensitivity to outliers (28). While medians are potentially more stable over time and thus possibly better indicators of long-term exposure than are means, it is unknown whether medians are a more valid metric for a 24-hour measurement. In the NCI/CCG study, the correlations between the mean and the 30th-70th percentile values were much higher (product moment correlation coefficient, $R > 0.88$) than reported in earlier studies (33).

There was some indication of stronger associations between childhood ALL risk and nighttime measurements than for the 24-hour summary measurements. The potential relevance of this finding is unclear, since the differences in risk estimates associated with the nighttime versus the corresponding 24-hour measurements were small and the confidence intervals overlapped substantially. However, children are more likely to be in their bedrooms during the night than during the remainder of the 24-hour period. Thus, it is possible that the nighttime measurement and the corresponding risk estimate may reflect children's residential magnetic field exposure more accurately than does the corresponding 24-hour measurement. The NCI/CCG monitoring data demonstrate less variability during the night, which is compatible with the risk estimates associated with the measures of central tendency. Constant magnetic field levels are typically generated by power lines and, perhaps, by electric blankets, while there is more variability associated with short-term exposures from most electrical appliances (34).

Similar to results of previous investigations (21, 26, 27), spot measurements in various rooms were not associated with the risk of childhood ALL. There was a reasonable correlation (product moment correlation coefficient, R, ranged from 0.62 to 0.85) between spot measurements and the 24-hour time-weighted average, but poorer correlation of spot measurements with percentiles (R ranged from 0.28 to 0.56) or nighttime measurements (R ranged from 0.50 to 0.52) using various metrics.

A nonmonotonic relation of cancer risk with magnetic field strength has been proposed (18). The results from the NCI/CCG study provided no support of a departure from linearity for any of the magnetic flux density indicators. The data did not permit an evaluation of the possible effects of harmonics (signals with several frequencies, with each being a multiple of the fundamental frequency) because the measurements covered only a limited range of frequencies. Electric fields were not measured in the NCI/CCG study because of the technical difficulty of relating electric field measurements to subjects' actual electrical field exposures (35). In addition, there was no indication at onset of the NCI/CCG study that electric field exposure was associated with leukemia in either children or adults (26, 36). Subsequently, only one study (37) among four evaluating the relation (21, 26, 29, 37) has reported an association between measured electric fields and the risk of childhood leukemia. Intermittency (or transients), i.e., very fast, irregular signals with a range of frequencies, has also been suggested as an alternative metric (3, 38). The NCI/CCG protocol was not designed to capture all events of extremely short duration. The rate-of-change metric, evaluated in the NCI/CCG study using data from meters placed at a fixed location, characterized temporal variability only for children's residential magnetic field exposures. In contrast, the rate-of-change metric, measured by Burch et al. (13) using meters worn by electrical utility workers, summarized a combination of temporal and spatial variability of occupational magnetic field exposures experienced as workers moved around in their work environment. Because of the different sources of variability, the rate-of-change (or the modified rate-of-change) estimates are likely to be greater when derived from data generated by meters worn by subjects than from data produced by meters in fixed sites. Thus, direct comparisons should not be made for results of the rate-of-change metric between the NCI/CCG study and that by Burch et al. (13).

The initial report from the NCI/CCG investigation concluded that the findings provided little support for the hypothesis regarding residential magnetic field exposures and childhood ALL based on time-weighted average summary measurements (6). In this report, various metrics that might be related to risk were examined more fully. The measures that showed the strongest association were those of central tendency, which includes the time-weighted average. Risk estimates for subjects in the highest exposure categories ranged from 1.02 to 1.69, with most risks below 1.50. Thus, the results do not change the fundamental conclusion from the previous report (6) that there was little evidence of an association between high magnetic field levels and risk of childhood ALL. The findings of this exploratory investigation suggest that future studies should focus on the median and other measures of central tendency.

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